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(54) Title: NEONATAL HUMAN BLOOD BANK AND HEMATOPOIETIC OR IMMUNE RECONSTITUTIONS PERFORMED THEREWITH

(57) Abstract

The utility of a human umbilical cord or placental blood bank for use in hematopoietic or immune system reconstitution is disclosed.

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NEONATAL HUMAN BLOOD BANK AND HEMATOPOIETIC OR IMMUNE RECONSTITUTIONS PERFORMED THEREWITH

Background of the Invention

In the period of 1965-1975, umbilical cord blood transfusions were given to 17 terminal patients who obtained some objective improvements. These cases were primarily malignancies. One reported case involved sarcoma [M. Ende, Pac. Med. Surg. 74 80-82 (1966)] and another, acute lymphoblastic leukemia. [M. Ende and N. Ende, "Hematopoietic Transplantation by Means of Fetal (Cord) Blood, a New Method," Va. Med. Monthly, Vol. 99, 276-280, March 1972].

The bone marrow transplant in the latter patient was shown to be successful by changes in blood groups. The patient had a clinical remission and survived for 13 months, at that time, an uncommon event. This cord blood human transplant was the first of its kind. Another successful such transplant has recently been reported (E. Gluckman et al., "Hematopoietic reconstitution in a patient with Fanconi's Anemia by means of umbilical cord blood from an HLA-identical sibling," N. Engl. J. Med. (1989) 21; 1174-1178).

The initiators of this approach to reconstitution recently reported further results indicating the viability of this new approach ["Fetal Cord Blood's Potential for Bone Marrow Transplantation," N. Ende et al., Life Sciences, Vol. 44, pp. 1987-1990 (1989)]. See, also, Broxmeyer et al., Proc. Natl. Acad. Sci. USA 1989; 86:3828-32, and WO 89/04168. The entireties of all these publications are hereby incorporated by reference.

Additional knowledge concerning the hematopoietic potential of cord blood has also recently been gained, including extensive ability to generate progenitors for secondary colonies and having them identified as present in human cord blood [A.A. Fauser and H.A. Miesner, Blood 53:1023-1027 (1979); T. Nakahath and M. Ogawa, J. Clin. Invest. 70:1324-1328 (1982); A.G. Leary and M. Ogawa, Blood, 69:953-956 (1987)].

To further demonstrate the potency of umbilical cord blood, N. Ende et al. have recently produced xenografts in relatively normal mice that had been radiated (to be published: "Production of Human to Mouse Xenografts by Umbilical Cord Blood," Ende, N. et al., Life Sciences, May 5, 1990). Prior to this, the only examples of human to rodent xenografts were performed on immune deficiency animals [D.E. Mosier et al., Nature 335:256-259 (1988); J.M. McCune et al., Science 241:1632-1638 (1988); S. Kaniel-Reid and J.E. Dick, Science 242:1706-1709 (1988)].

Summary of the Invention

The time has arrived for providing benefit to mankind from successful hematopoietic or immune transplants based on administration to humans of neonatal blood, including umbilical cord blood and/or placental blood, preferably umbilical cord blood. Such transplants can be utilized in a wide variety of applications, including all instances where bone marrow transplants have heretofore been indicated. In view of the high percentage of stem and progenitor cells in neonatal blood, this approach has greater potential for benefit than even bone marrow per se. In addition, of course, this invention is also applicable to experimental procedures involving hematopoietic reconstitutions, e.g., all those equivalent to bone marrow transplants. (In general, herein, wherever hematopoietic transplants are discussed, all other transplant types which can be effected by this invention are also included.)

In order for the benefit to mankind to be realized, a variety of aspects must be well planned and both ethically and scientifically acceptable. In one aspect, consequently, this invention relates to a human umbilical cord or placental blood deposit, storage, and retrieval bank consonant with both ethical and scientific requirements. For example, the blood bank of this invention will not store samples of a donor's blood according to conventional blood storage principles, e.g., wherein the blood is stored in a single container for therapeutic use in association with a relatively much smaller container, hereinafter a pilot volume (or pilot subvolume). The latter pilot subvolume is conventionally retained for purposes of identification and/or verification/typing of the blood stored in the therapeutic-size sample. Rather, a key feature of this invention is that the umbilical cord or placental blood will be stored in a multiplicity of independent sample subvolumes (which are not merely pilot subvolumes) useful therapeutically. Of course, co-storage of pilot subvolumes, along with the therapeutic subvolumes, is not excluded in this invention.

With this form of storage, the ethics of the donor/recipient interaction becomes greatly facilitated. For example, at least one stored subvolume can be irrevocably maintained solely for purposes of administration to the human donor for any eventuality which may occur in the future. The remaining subvolumes can be designated as available for subsequent use for the benefit of a human individual other than the donor. In this way, for example, a newborn's mother and/or father or guardian will not be faced with the choice of whether to permit the newborn's blood to be stored for the purposes of administration to another person other than the newborn. Instead, in one possibility, there can be a requirement on a blood bank of this invention that all blood donated or sold thereto must be stored in a

multiplicity of subvolumes, at least one of which must be reserved for possible future use by the donor individual. As a result, the ethics of the situation is greatly alleviated since a newborn's parent or guardian is never faced with even the possibility of selling all of a newborn's blood for the benefit of humans other than the newborn, thereby foregoing the potential future benefit to the infant of his own neonatal blood. In other words, in accordance with this invention, all stored blood remains available for both the donor individual and others. This feature will greatly contribute to the medical, scientific, psychological, and ethical success of the bank of this invention and the resultant hematopoietic transplants which ensue, as well as the acceptability of the entire concept of such a bank and such reconstitutions to the public, in general.

Accordingly, in one aspect, this invention relates to a human umbilical cord or placental blood deposit, storage, and retrieval bank comprising:

a plurality of storage-stable samples from different donor humans of human umbilical cord or placental blood components,

a sample from a particular human donor individual being stored in a multiplicity of independent sample subvolumes other than a pilot subvolume, said subvolumes being of a size adequate for therapeutic use of said blood component subvolumes, and

said samples being indexed for accurate identification and retrieval.

In preferred aspects, the blood component samples will comprise umbilical cord blood components only or, perhaps, mixtures of umbilical cord blood components with components from placental blood. In a preferred aspect, the blood samples will be stored in a frozen (cryopreserved) state. The samples are preferably indexed for identification according to both the identity of the human donor individual (e.g., the name or number

associated therewith) and/or the type of the blood sample (e.g., the major blood group type, HLA tissue type, etc.). The bank will also preferably have associated therewith means for physically retrieving a particular sample according to that sample's index criteria, e.g., human donor identity or blood type. Further preferably, the stored samples will be of whole cord or placental blood or of a subportion thereof, e.g., a portion particularly high in progenitor and/or stem cells, which have been separated from the remainder of the whole blood.

In a further aspect, this invention relates to a method of effecting a hematopoietic and/or immune reconstitution of a human, comprising retrieving from a blood bank of claim 1 a subvolume of umbilical cord or placental blood components which substantially matches the blood type of the human to be reconstituted, and introducing into said human said substantially matched blood component subvolume, whereby said reconstitution is effected.

The same preferences mentioned above with respect to the bank, of course, also relate to the blood used in the foregoing method. In further preferred aspects, the host receiving the reconstitution will be different from the donor from whom the blood sample was derived. Of course, it is also possible, as mentioned above, for the reconstitution to be autologous, i.e., for the donor and the host to be identical.

In view of this invention, many of the present deficiencies associated with bone marrow transplants can be overcome.

With the advent of commercialized bone marrow transplants some 20 years ago, it became necessary to support this effort with a registered file of bone marrow donors. However, it has been most difficult to enlist donors. For example, there are some risks, the donating process creates discomfort, and the donor is required to

spend at least one night in the hospital. As a result, the current system is far from adequate, and there are too few donors--less than 500,000 in the world. Consequently, the chance of a type match (necessary for a transplant) is in the area of 1 in 20,000 due to the variability of the tissue typing and blood group antigens.

Further indicating the difficulty, a National Registry for bone marrow was formed in 1987. Two years later, it has only 90,000 donors, even after annexing several satellite registries through the U.S. Recently, there are 10,000 patients in waiting. Unfortunately, the chance for a match for these patients at the existing rate of incoming donors is not high. Moreover, because of cost, only partial HLA testing of a donor is completed at the outset. This requires the waiting patient to go through a difficult psychological period while waiting weeks for the final tests to be conducted. Finally, because of the low chance of success, a registry containing 50,000 registrants may only help 5 or fewer patients in a year. This represents only a small fraction of the need for leukemia alone; yet there are so many other possible applications for bone marrow transplantation that go unheeded. Furthermore, experimentation is practically impossible.

This invention will alleviate or eliminate these defects in the present system. By simply harvesting and storing umbilical and/or placental blood, painlessly and with minimal effort, from a reasonable percentage of the newborns born each year in the U.S. alone and, preferably, of course, worldwide, in a short time period, millions of samples from individual donors can be gathered and stored according to any desired indexing parameter, including donor identity, blood type, etc. Such a large variety of individual samples from different human beings will greatly increase the chances of finding a successful match between host and donor. Except for

unusual cases, once the number of samples reaches well into the millions, which should occur in a relatively short time frame, the expectation should be that a match will be essentially ensured, in contradistinction to the current situation where precisely the opposite result is the norm. Furthermore, there will be no inconvenience whatsoever to either the newborn or the mother during the harvesting process since only the umbilical cord and/or placenta need be involved. It is expected that a large number of parents or guardians will agree to donate the umbilical and/or placental blood since the latter presently is simply a waste product and since with the guarantee of this invention that at least one subvolume will be reserved solely for use of the newborn, there should be a high incentive to agree to the donation and storage of the blood.

In synopsis, steps involved in this invention include the following:

- **Harvesting**

The mother, parents, or guardian (preferably with the advice of the obstetrician) will agree to donate the cord blood to a bank of this invention in accordance with the foregoing discussion. Thus, the mother will preferably be guaranteed the permanent retention of an adequate portion (subvolume) of the donated blood throughout the lifetime of the newborn in case a need arises. In turn, the remainder of the blood may be used (stored) as is, processed by separation techniques, grown (from a portion thereof, for example) to a larger sample by processes now being perfected by several organizations, e.g., Marrow Tech, Inc. of Albany, New York (USP 4,721,096), etc. In this way, transplantation material will be available for the public at an affordable cost.

Transportation

The cord and/or placental blood can be transported to and from the bank of this invention any conventional containers for blood, e.g., in electronically controlled containers, preferably by express methods or messengers. The militaries of the U.S. and other countries have been using such containers in war zones for many years. One example is the Biological Blood, Vaccine, and Drug Storage and Transportation Refrigerator/Heater No. M-50BT used by the Israeli and British forces and also on order for trials in the U.S. military. Such containers are available from the Segnetron Company of Edison, New Jersey.

Such containers can be controlled by a thermoelectric heat pump utilizing the Peltier effect. The direction of the current basically controls the temperature within minute limits consistently over long periods of time and is essentially maintenance free. Such units are currently available in a variety of sizes, including small ones the dimensions of a briefcase and can be battery operated.

Storage and Retrieval

The subvolumes of cord blood to be retained for the donor will preferably be stored in a refrigerated area separated from the refrigerated area for the samples for the public, i.e., humans other than the donor. Of course, where logic and/or technology admits or prefers, all subvolumes of a given sample from a human individual can also be stored in the same refrigerated area. Fault tolerance computers and redundant systems will preferably be used throughout to eliminate catastrophe and provide a fail-safe system. Current advanced technologies utilizing the conventional principles of Computer Integrated Enterprise (CIE) can enable a safe, smart, and friendly system that will perpetuate an efficacious, inexpensive product for those in need thereof.

Such conventional technologies which can be utilized including Machine Vision (MV), Robotics, Automated Guided Vehicle System (AGVS), Automated Storage and Retrieval Systems (AS/RS), Computer Integrated Manufacturing (CIM), Computer Aided Process Planning (CAPP), Statistical Process Control (SPC), etc.

All of these technologies are available and can be routinely developed and/or adapted, e.g., in consultation with the Society of Manufacturing Engineers, Dearborn, Michigan. Such methods and equipment can provide a storage and retrieval system of a high confidence interval. Of course, the invention also includes less sophisticated banks using, e.g., simple, very large area refrigerators maintained at necessary temperatures, containing numerous racks (e.g., simple shelves) on which are indexed and stored the samples and subvolumes of this invention. Using any conventional index system, retrieval can be simply effected by a human walking to the proper indexed shelf and selecting the identified matching subvolumes. This invention is also not limited to frozen (cryopreserved) samples, but also includes any reliable technique for long-term storing of the blood of this invention, e.g., including storage of stem and/or progenitor cells, e.g., with amino acids, inosine, adenine, etc. Storage with any substance that can prolong the shelf life of the cord or placental blood is included. Work is currently being evaluated in existing Red Cross blood banks.

Since approximately two to three million babies are born each year in the U.S. alone, this invention, which is based on cooperation with the public in at least two directions, will provide a quantum leap into the future for hematopoietic transplantation medicine. In one direction, it provides reliable protection to the mother and newborn at little or no cost. In a second direction, in a short time, the invention will provide millions of samples of transplantable blood available to the public

at minimal cost. Furthermore, many of the ills of the current registry system will be overcome. The donor is no longer threatened and inconvenienced. Complete HLA testing can be conducted at the harvesting site (or elsewhere, at choice, e.g., the storage site) and the applying patient will be able to receive an immediate response from the bank of this invention and/or an administration system managing and coordinating the bank.

In certain situations, it may be necessary to type the baby before birth. In such cases, techniques can be used which now exist for obtaining samples of blood or amniotic fluid from a fetus.

Importantly, as mentioned, there will be millions of samples available which will increase tremendously the occurrences of matches. As a result, the use of bone marrow transplantation, or more properly, of lymphoidic and hematopoietic transplantations of this invention, should be proliferated to a level that will enable new cures for a great number of fatal diseases now out of control.

In the context of this invention, the term "bank" has no particular limitations other than those explicitly mentioned herein. Thus, no particular types of association among the various samples and subsamples is required as long as the characteristics described herein are met and/or achieved. The term "plurality of samples" refers in the most generic sense to at least two samples of blood, each from a different human. There is no upper limit on the number of samples which can be contained in a given bank. Of course, it is preferred that there be millions of samples from corresponding millions of human donors. The term "samples" refers in general to all of the umbilical cord and/or placental blood from a single individual human donor. This sample of an individual's blood will be separated into a multiplicity of sample subvolumes for the purposes described above. The term "multiplicity" also refers to at least two subvolumes of

a given sample of blood from a particular individual. The number of subvolumes can vary in accordance with the technology at a given time, e.g., in accordance with the minimum volume considered safe and effective for a particular therapeutic use. Generally, the size of such subvolumes will be greater than the volume of a typical pilot tube currently used in conjunction with storage of whole blood donated for current peripheral blood banks.

Typically, these "therapeutic" subvolumes will be substantially equal in size, but this is not necessary. Storage of subvolumes of different sizes is fully within the scope of this invention, e.g., storage of subvolume size for the donor could be larger than the subvolume size(s) stored for potential hosts. Were it to become technologically feasible that the current volume of a pilot container would become useful for therapeutic use, under such circumstances, the term "multiplicity" will refer to a minimum of three sample subvolumes, one for purposes of the typical pilot tube (e.g., measurement of identifying and characterizing parameters) and the other two for the therapeutic purposes of this invention. Thus, these two terms, "multiplicity" and "pilot", are defined in conjunction with one another in the sense mentioned above.

The term "storage-stable" refers to a sufficient stability under the conventional physical conditions of storage such that the thus-stored blood retains viability for the therapeutic purposes discussed herein upon retrieval from the bank of this invention and any subsequent treatment necessary for rendering the blood effective for administration to a human, e.g., thawing in the case of a frozen blood bank. The typical length of time of stable storage of a given sample in the blood bank will, of course, vary with the demand which ensues, both in general and for blood of particular types. However, with a routine rotation schedule, it is expected that the typical non-autologous blood sample will be

stored for a period of time on the order of 1-10 years, shorter and longer durations, however, being perfectly suitable in accordance with this invention since there is no criticality in the length of time blood is stored, e.g., under conventional cryopreservation conditions and procedures; see, e.g., W. Nothdruft et al., Scand. J. Haematol. 19 470-481 (1977); F.E. Zwaan et al., Bluut 45 87-95 (1982); and S.C. Sarperl et al., Int. Soc. Exp. Hemat. 7 113-120 (1979).

If cord blood can be properly matched rapidly and transported, it may not be necessary to freeze all the portions (subvolumes). In an equivalent aspect of this invention, if enough specimens are available, it may not be necessary to freeze the donor's original portion if it can be guaranteed that an exact replacement is available as a substitute therefor and will be irrevocably dedicated to the donor.

Suitable containers for the blood of this invention during storage will include any conventional container compatible with both the blood and the storage conditions, e.g., containers presently used for storage of presently banked blood, e.g., by the Red Cross. Suitable containers can be fabricated from conventional polymers currently used for this purpose and can have any convenient shape and/or volume consistent with this invention and this disclosure.

By the term "independent" in conjunction with sample subvolumes is simply meant that each subvolume will be independently retrievable from other subvolumes of a given sample from a particular individual. The subvolumes can be stored, as mentioned above, in different locations from each other within the bank, in different refrigerated containers within the bank, together within the bank (either in contact with one another or not in contact with one another, etc.), and generally in any configuration consistent with the

overall structure, operation, and logic of a given bank system.

An additional advantage of banking the blood of a particular single sample using the subvolume approach of this invention is that in situations where it is desired to use only a portion of the original full sample, this invention will avoid an additional freeze/thaw cycle, with its attendant additional inconvenience of physical manipulations involved and, most importantly, with its additional likelihood of adverse effects on the blood.

Typically, the subvolumes of a given sample which will be adequate for a therapeutic use will be in the range of 10-75 ml, the precise amount being variable with respect to class of patient, disease being treated, state of technology at the time, etc. Furthermore, depending on the number of samples in a bank of this invention at a given time, it can be decided that a given sample will be divided only into two or three or four or five or six, etc. subvolumes, irrespective of the minimum quantity needed for prevalent therapeutic uses, e.g., because of the current supply in the bank for blood of the type of the particular sample concerned.

Each sample and, individually, each subsample thereof (i.e., subvolume) will be indexed in a manner for reliable and accurate identification and retrieval. The nature of the indexing system, both from a logical and physical manipulative viewpoint, is not critical for this invention as long as it is reliable and accurate. Many conventional systems will suffice. For example, each container for each subvolume can be marked with alphanumeric codes, bar codes, and any other cognizable method or combinations thereof. Apart from the bank and/or at the bank, there will also be an accessible and readable listing of information enabling identification of each subvolume and its location in the bank and enabling identification of the source and/or type of the blood in each subvolume. The system can be operated

manually, e.g., using a simple ledger system, or, most preferably, utilizing a computer and conventional software such as data base management and spreadsheet programs.

With more particularity, the steps involved in carrying out the invention of this application are discussed below.

In one feasible scenario, a physician and a pregnant patient confer. The physician will outline a proposition such as follows: A bank of this invention will, at minimal or no cost, store a sample (subvolume) of the forthcoming newborn's umbilical cord and/or placental blood for the life of the newborn to provide a life-permanent supply of cells for hematopoietic reconstruction if unfortunately ever necessary. Perhaps approximately half, for example, will be retained for the newborn, with the remainder retained for public availability.

The major portion of the remainder can be stored to be available for transportation for subsequent use (experimental, e.g., research, or therapeutic) and a smaller portion for a pilot tube. A pilot tube is defined conventionally, e.g., an aliquot specimen for laboratory testing using known and future methodologies providing information of use, e.g., medically for the donor or host.

Both the major subvolumes and the pilot tube are indexed, e.g., labeled, usually identically, with all desired and/or necessary parameters. For example, there can be a universal code number system that will be controlled by the administrator of the bank and used to identify all subvolumes and correlate each with patient information. Preferably, the tube will be marked with at least its code number from the system. Any of the pertinent information correlated with the code number can also be on the label or other marking method, e.g., name, sex, and weight of donor; name and address of parent or

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	Clinics in Haematology, vol. 15, No.1, issued February 1986, N. Gorin, "Collection, Manipulation and freezing of Haemopoietic stem cells". pages 19-48, see entire article.	1-15

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

guardian; date and time of delivery; blood group and HLA identification; nature of contents, e.g., whole blood, partial blood components only; etc.

After sufficient information is conveyed to the prospective parent or guardian to enable informed consent, the latter will give assent, e.g., by signing a proper document, e.g., in the presence of witnesses. At the time of delivery, normal, caesarian, or otherwise, preparations will be carried out to collect the umbilical cord and/or placental blood. After the baby is delivered and while the placenta is still attached to the mother's uterus, the umbilical cord is clamped and cut. The baby is removed from the field. The umbilical cord clamp downstream from the placenta is then released while the cord blood flows into an appropriate conventional sterile container.

In addition to relying on gravity flow, it is preferred to increase harvest yield by using pressing/milking procedures and specialized equipment. This can improve the harvest by 20-30%. For example, after delivery of the baby and after the major sample portion has been collected by gravity flow, the placenta can be placed in a mechanical press. A suitable press will contain a variable drive whereby the pressure and closing speed can be accurately controlled. Consequently, by gently compressing the placenta, an additional harvest can be obtained by clamping a small pump at the discharge point of the umbilical cord to create suction or negative pressure, further aiding the efficiency of the harvest.

The cord blood can be combined with conventional components commonly used in the collection of bone marrow for transplantation purposes and/or in the collection of blood. These include but are not limited to the following: citrate-phosphate-dextrose (CPD), acid-citrate-dextrose (ACD), heparin, antibiotics, substances which may improve survival of the cells, etc. After

collection, the blood can be transported to testing facilities in the hospital, a regional public bank, or the bank of this invention.

When testing within the confines of a hospital, the material should be immediately hand-carried to the testing site and retained under proper conditions, e.g., as are well known and/or described herein. When testing at a regional public bank, an appropriate container, such as the Biological Blood, Vaccine, and Drug Storage and Transportation Refrigerator/Heater No. M-50BT available from Segnetron Company of Edison, New Jersey, should be used for transportation. The same holds true when transporting the harvested samples to be tested at regional, national, or worldwide centers which are banks of this invention.

Once the material has arrived at the testing site, the pilot tube will be conventionally examined and/or analyzed for blood groups, bacterial and viral contamination (e.g., HIV, syphilis, hepatitis, etc.), the complete HLA system, DNA identification, and any other typing characteristics, including any further new characterizing indicia developed in the future such as endothelial cell antigens (see, e.g., The Clinical Significance of the Vascular Endothelial Cell Antigen System, Brasile et al., February 1985, Transplantation Proceedings, Vol. XVII, No. 1); The Vascular Endothelial Cell - Specific Antigen System, Cerilli et al., February 1985, Transplantation Proceedings, Vol. XVII, No. 1; The Vascular Endothelial Cell Antigen System, Cerilli et al., Transplantation Proceedings, Vol. 39, No. 3, March 1985), inter alia.

Unless a sample to be used for transplantation were immediately to be rushed from the hospital or test site to an awaiting transplant candidate, the thus-measured parameters would be permanently stored for purposes of the banks of this invention. Of course, were the testing to show some defect in the particular sample, e.g., a

positive test for HIV, hepatitis, etc., the sample would be discarded or utilized for research purposes or experimental use.

Thus, the term "type" or "typing", as used herein, has its broadest meaning and refers to any and all characteristics of a blood sample which might be of relevance or importance for any potential use of the blood sample. The term and the corresponding testing conducted to determine the "type" of the blood is thus not limited to any particular tests mentioned herein. Determination of which tests are relevant and how to perform them is entirely conventional and will, of course, change with technological developments.

This can be accomplished conventionally by integrating the hospital computer system with that of the bank of this invention, e.g., by conventional on-line telecommunication (modem) hookup. Immediate shipping could be arranged for return to the hospital if an emergency existed.

The blood stored in the bank of this invention can be whole blood or any portion or portions thereof. Like normal blood, cord and/or placental blood has a variety of component entities. These entities can be fractionated or otherwise separated from one another using conventional separation techniques, common in conjunction with normal peripheral blood. Similarly, there also exist conventionally utilized various fractionating procedures in conjunction with bone marrow. These can also be applied highly analogously to the cord and/or placental blood of this invention. Fractionation of the blood involved in this invention can occur either prior to entry into the depository or subsequent to retrieval therefrom.

With respect to the primary use of the blood of this invention, i.e., hematopoietic reconstitutions or lymphoid reconstitutions, the preferred fraction of the blood will be that which contains the cells which are

effective for causing the reconstitution to occur. Primarily, these are the stem cells and the progenitor cells. Consequently, in one aspect of this invention, instead of or in addition to whole blood, there will be banked a fraction of the cord and/or placental blood high in concentration of the stem cells and/or progenitor cells. Any other component of the whole blood can also be banked in accordance with this invention. Where a variety of fractions is banked and/or both subvolumes of whole blood and of fractionated blood are stored, additional conventional indexing can be utilized in conjunction with this disclosure to produce a reliable and accurate system for storing and retrieving the appropriate whole blood or fraction subsample.

As also discussed herein, it is possible to use the sample donated by a human at least partially for the growth of additional desired blood cell components using state-of-the-art techniques. This growing procedure can also be employed before or after the deposit, whereupon this invention also includes the banking of such blood or components thereof grown from the initially donated sample.

When the sample arrives for storage at the bank of this invention, there will be for each donor one pilot tube plus two or more subvolumes. At this point, a standardized labeling procedure can be employed, e.g., as follows. The established code number can be reproduced on a label (e.g., at the top of the container) on its closure. A new label can be prepared and affixed to the opposite side of the container and can include all or a selected portion of the original information gathered about the sample. Thus, there can be three labels, all correlated with one another: the original from the hospital, the new one prepared by the registry/depository (bank) and a top label with the existing code number. The existing code number can simultaneously designate a unique sample location in the depository.

The two or more major subvolumes are sent by a conventional programmed conveyor to a storage tray location according to the code number. Conversely, the pilot tube can be sent by the same method to a different storage tray in a special area for pilot tubes, according to the code number. An AGVS can be used to travel throughout the storage area, placing the containers in the designated trays and locations within the trays. This AGVS is conventionally equipped with robots and a machine vision system, which can be utilized as follows.

The samples can be stored in trays stacked in racks from the floor to the ceiling. The AGVS travels in a programmed pattern according to the entry data at the receiving station of the depository. When the labels are prepared and the samples entered to the conveyors, the AGVS is automatically sequentially programmed. It performs, inter alia, the following functions:

1. The machine vision camera is located on the robot's wrist. It raises the camera to tray facing and reads the nomenclature thereon. It then waits for confirmation from the computer before taking the next step.

2. After confirmation, the tray is pulled out to a position where its storage sites are accessible. The robot arm then moves to the proper container on the adjacent conveyor, stops, and, with the wrist camera, verifies the code number of the top for the container. It then waits for confirmation from the computer before taking the next step.

3. After confirmation, the container is grasped and placed in its proper location on the tray. However, before releasing the container, it holds for a small increment of time to once again receive confirmation that the code number and selected location are indeed synchronous.

4. After confirmation, the AGVS releases the container, closes the tray drawer, and moves on to the next assignment.

An AGVS is an automated guided vehicle system which is a programmed carrier which transports goods from point to point (see, e.g., Automation Encyclopedia, Society of Engineers, Dearborn, Michigan 1988). Machine Vision is a process in which information is extracted from visual sensors to enable machines to make intelligent decisions. A robot is a reprogrammable multi-functional manipulator designed to move material, parts, tools, or specialized devices through variable motions for the performance of various tasks. See, e.g., Automation Encyclopedia, supra, as well as conventional technology providable by RIA, the Robotics Industries Association, founded in 1974, including:

AS/RS: Automated Storage and Retrieval Systems, an overall nomenclature given to the architecture and configuration described in literature such as the Automation Encyclopedia;

CIM: Computer and Integrated Manufacturing, the integration of a process by computers, also discussed in the Automation Encyclopedia;

CAPP: Computer aided process planning, referring to activities associated with planning, e.g., in this case, the process of handling a container. Also see the Automation Encyclopedia; and

SPC: Statistical Process Control, a computer system allowing for economically sound decision-making about actions affecting a process. See Automation Encyclopedia, also.

When a request for a match or near match is received by the bank/registry and depository, it can be handled as follows:

1. A computer search of the inventory is conducted. The requestor is notified immediately of what is available.

2. When an order is received, the AGVS on floor is programmed to retrieve a designated container and pilot tube.

3. The retrieval procedure can be as follows: The AGVS travels to the designated tray/drawer. The MV wrist system confirms the drawer number and awaits confirmation by the computer. The AGVS then opens the drawer.

4. The robot arm travels to the location and, with wrist MV, reads the code number on top of the container and awaits computer confirmation.

5. The robot grasps the container and carries the load to a second MV system at its base and allows that system to verify the nomenclature on the label provided by the bank. After computer confirmation of all this quality control data (SPC), the robot places the container in the programmed conveyor system, which carries the containers to the distribution department.

6. In this final stage, the container can be visually checked by human intervention against the order to create a final inspection and control before shipping.

This AR/RS, Automated Storage and Retrieval System can be conventionally maintained at appropriate temperature (nominally -70°C). For example, conventional techniques that are currently available for freezing human bone marrow can be employed.

Conventional built-in reducing and fault tolerance features can be incorporated such as use of a fault tolerance host computer, e.g., an ST status computer; multiple personal computers; multiple refrigeration compressors; in case of power failure, fuel-fired generators; multiple MV and AGVS; etc.

When shipping the sample, and, e.g., combined therewith a portioned pilot tube, to the recipient, the same basic methodologies can be followed, as described with respect to transportation. In one mode, the total pilot tube contents will not be shipped. Only a portion will be sent, while the remainder will be returned to the

original storage location to be used for future shipments. The portioning work is accomplished in the shipping department and returned to the AS/RS through the same fail-safe system already described. Alternatively, at the outset (after harvesting), a separate pilot tube (of a size adequate for the above-mentioned distribution purposes, i.e., the portion maintained above) can be filled for each subvolume to be stored. In this way, the extra handling needed for special thawing and refreezing of a single pilot tube's contents can be avoided.

Various types of orders can be received, including;

1. those where the recipient is the original donor;

2. those where the recipient may have one of many diseases that require a bone marrow transplant where a cure or partial therapeutic relief may result with an exact match or one as exact as technically available;

2. those where the recipient may require a near-match as more favorable as opposed to an exact one. In this case, an exact match may endanger the recipient since the transplanted cord blood may take on the disease of the host. Consequently, a near match may be more protective to the recipient [Successful Allogenic Transplantation of T. Cell, R.C. Ash et al., Journal of Medicine, Vol 322, No. 8, February 1990; and Hematopoietic Transplantation by Means of Fetal (Cord) Blood, M. Ende and H. Ende, The Virginia Medical Monthly, Vol. 99, 276-280, March 1972]. With the CAPP, Computer Aided Process Planning, any combination of needs can be accommodated, providing the proper material is in inventory.

The term "match", as used herein, has its normal conventional meaning, as used in conjunction with current bone marrow transplant considerations. The "degree" to which important blood parameters need be identical will vary from patient to patient, from disease to disease, and from year to year, depending on the current state of

technology. The important point is that the bank of this invention will be able to provide a subvolume of the desired blood having the desired degree of match in view of the large number of samples expected to be involved.

As stated above, it is a fundamental aspect of this invention to retain a major portion of a sample (subvolume) for the lifetime of the donor while using the remainder of the donated blood for the public benefit and for a pilot tube(s). It is also within this invention to use some of the blood to grow stem cells, progenitor cells, or other of its components into larger samples using techniques such as those of Marrow Tech Company in Albany, New York.

Theoretically, the banked blood of this invention can be used in a similar manner and application as bone marrow, e.g., for hematopoietic reconstitution, which generally is intended to include reconstitution of any function with which the blood is connected, including immune system reconstitutions.

The application of cord and/or placental blood in bone marrow transplantation (hematopoietic reconstitution) has innumerable uses, some non-limiting examples of which are genetic congenital disorders, disfunction of normal blood cell production, toxic and radiation exposure, malignancy of the hematopoietic and the reticuloendothelial system, auto-immune diseases, congenital defects of immunity, survival of patients with neoplasm in which massive chemotherapeutic or radiation has been utilized and a bone marrow transplant is necessary, and many others. See, e.g., Bone Marrow Transplantation, R.P. Gale, Critical Reviews in Oncology/Hematology 23, 261-296, 1985; The Application of Bone Marrow Transplantation to the Treatment of Genetic Diseases, R. Parkman, Science, Vol. 232, 1373-1377, June 1986; Overview of the Clinical Relevance of Autologous Bone Marrow Transplantation, F. Applebaum, S. Buckner, Clinics in Hematology, Vol. 15, No. 1, February 1986;

Bone Marrow Transplantation for Correction of Severe Aplastic Anemia and Primary Immunodeficiency, E. DuPont et al., Annals of Clinical Research 13:358-366, 1981; Bone Marrow Transplantation in Acute Leukemia, G. Santos and H. Kaizer, Seminars in Hematology, Vol. 19, No. 3, July 1982; Bone Marrow Transplantation, J.C. Biggs, Aust N.Z., J. Med Vol. 10, 669-677, 1980; etc.

Many additional uses can be expected to develop in the areas of diseases that do not deal directly with the hematopoietic, lymphoid, or reticuloendothelial systems, but may be related to antigen-antibody reactions or cell-mediated immune reaction or allergic reactions of a host of yet-to-be-defined causes. Whenever reconstitution of blood or immune function is indicated, this invention will be applicable.

A partial, non-limiting listing of such types of problems includes multiple sclerosis, amyotrophic lateral sclerosis, any type of allergic encephalitis in which antibody reactions are producing injury to tissue, renal diseases where immune deposits play a role, specifically, for example, renal diseases which recur in transplanted kidneys, etc.

Moreover, specific, selected specimens of the cord or placental blood banked per this invention (or cells or components derived therefrom) may be utilized in association with any organ transplant. In fact, it has been predicted that one day, marrow (cord or placental blood) cells may accompany any kidney to be transplanted. A.P. Monoaco et al., Transpl. Proc. 6 1207-1212 (1988). The only reason this work has not been completed is the current scarcity of marrow. The advent of the registry/depository of this invention will alleviate this problem. Practically all organ systems have been related in one way or another to diseases in which antigens and antibody play a significant role. These diseases may be modified, arrested, or cured with a newly reconstituted immune system which could potentially be obtained from

umbilical cord or placental blood preserved in a bank of this invention. Even a disease such as schizophrenia is a possible autoimmune disease (see R. Ganguli, B.S. Rabin, R.H. Kelly, 1987, "Clinical and Laboratory Evidence of Autoimmunity in Acute Schizophrenia," Annals of the New York Academy of Science 496:676-85). It is even theorized that the aging process itself may be significantly beneficially modified by a cord or placental transplantation.

Another use is in xenografts. For example, by the use of umbilical cord and/or placental blood, it may be possible to produce a human-to-animal graft in a specific animal model of a human disease state and allow testing of that disease to occur in the animal system. There are multiple animal models of human disease in which this test system can be instituted. (See, e.g., D.F. Patterson et al., "Research on Genetic Diseases: Reciprocal Benefits to Annimals and Man," 1988, JAVMA 193(9):1131-1144.) Xenografts of a human system to animals may be effective in curing these animals of any hematopoietic, lymphoid, immune, or immune-related disease. Moreover, umbilical cord blood may be xenografted to animals to produce human hematopoietic products such as blood, white cell components, and platelets. Also specific, entire human immune systems and reconstitutions may be created, which could thereby be used for transplantation into humans. Viability of a human-to-animal graft may depend on being able to suppress graft versus host response of the animal to the graft; however, because of the extreme difference that exists in a xenograft, graft versus host may not occur. This is an advantage. Regarding xenografts, see, for example, Production of Human to Mouse Xenografts by Umbilical Cord Blood, N. Ende et al., Life Sciences, May 5, 1990 (to be publisned).

Another potential advantage of cord and/or placental blood is based on findings that this material possesses a

greater potency value as compared to bone marrow. Fetal Cord Blood's Potential for Bone Marrow Transplantation, N. Ende et al., Life Sciences, Vol 44, pp. 1987-1990 (1989); T. Nakahata and M. Ogawa, J. Clinl Invest. 70:1324-1328 (1982); A.J. Leary and M. Ogawa, Blood 69:953-956 (1987); etc. The advantages of this fact can be numerous. For example, a single umbilical cord sample may apply to a greater number of recipients, since a lesser amount will be required for each transplant. Moreover, there is data to support the premise that multipotential progenitor cells exist in umbilical cord or placental blood. In some studies, 100% of the primary colonies obtained from cord blood had the ability to generate secondary colonies. As a result of the reported experiments, it can be estimated by that cord blood may well possess as much as 10 times or more the colony-forming ability of bone marrow per se. Accordingly, the reconstitutions based on blood derived from a bank of this invention can be carried out highly analogously to reconstitutions using bone marrow per se. Such details are highly conventional. Any differences attributable to the higher potency of the blood of this invention could produce advantages as discussed above, e.g., in the sense that lesser amounts might be utilizable in a given case where it is desired to use less than a given subvolume as stored in the registry/depository of this invention.

This application also relates to the invention of banking (depositing, storing, and retrieving) neonatal (e.g., cord and/or placental) blood in any fashion, in any scenario, for any reason, and particularly for purposes of performing reconstitutions for donors and/or non-donor hosts. In this regard, corresponding details of such a bank and reconstitutions are analogous to those described herein and in the publications cited herein, which are also incorporated by reference herein in this regard.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the disclosure in any way whatsoever.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A human umbilical cord or placental blood deposit, storage, and retrieval bank comprising:

a plurality of storage-stable samples from different donor humans of human umbilical cord or placental blood components,

a sample from a particular human donor individual being stored in a multiplicity of independent sample subvolumes other than a pilot subvolume, said subvolumes being of a size adequate for therapeutic use of said blood component subvolumes, and

said samples being indexed for accurate identification and retrieval.

2. A human umbilical cord or placental blood bank of claim 1, wherein said blood component samples comprise umbilical cord blood components and are stored in a frozen state.

3. A human umbilical cord or placental blood bank of claim 2, wherein said blood component subvolumes from a particular human individual are substantially equal in size.

4. A human umbilical cord or placental blood bank of claim 3, wherein the number of said blood component subvolumes is two.

5. A human umbilical cord or placental blood bank of claim 2, wherein said samples are indexed for identification according to the identity of the human donor individual and/or the type of the blood sample.

6. A human umbilical cord or placental blood bank of claim 5, further comprising means for physically retrieving a particular blood component sample according to the identity of its donor human individual or its blood type.

7. A human umbilical cord or placental blood bank of claim 5, wherein the blood component sample is indexed according to HLA tissue type or blood group.

8. A human umbilical cord or placental blood bank of claim 2, wherein blood samples are whole cord or placental blood.

9. A human umbilical cord or placental blood bank of claim 2, wherein cord or placental blood component samples consist essentially of progenitor cells or stem cells which have been separated from other components of the whole blood.

10. A human umbilical cord or placental blood bank of claim 2, wherein at least one of said subvolumes is indexed for retrieval only by its particular donor human.

11. A method of effecting a hematopoietic and/or immune reconstitution of a human, comprising retrieving from a blood bank of claim 1 a subvolume of umbilical cord or placental blood components which substantially matches the blood type of the human to be reconstituted, and introducing into said human said substantially matched blood component subvolume, whereby said reconstitution is effected.

12. A method of claim 11, wherein said human to be reconstituted is a different individual from the human individual who was the source of said substantially matched blood component subvolume.

13. A method of effecting a hematopoietic and/or immune reconstitution of a human, comprising retrieving

from a blood bank of claim 2 a subvolume of umbilical cord or placental blood components which substantially matches the blood type of the human to be reconstituted, and introducing into said human said substantially matched blood component subvolume, whereby said reconstitution is effected.

14. A method of claim 13, wherein said human to be reconstituted is a different individual from the human individual who was the source of said substantially matched blood component subvolume.

15. A method of claim 13, wherein said human to be reconstituted is the same individual as the human individual who was the source of said substantially matched blood component subvolume.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/02803

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) A61K 35/14; U.S. Cl. 435/2; 424/529

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
U.S.Cl.	435/2; 424/529

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

APS, WORLD DATS, SEARCH TERMS: BLOOD, PLACENTAL, UMBILICAL, NEONATAL, FETAL, STEM CELLS

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X,P	US,A, 5,004,681 (Boyse et al.) 02 April 1991 see entire document	1-15
Y	Science, Vol. 168, issued 22 May 1970, P. Mazur, "Cryobiology: The freezing of Biological Systems" see pages 939-949, 942, Fig.2.	2
Y	Cancer, vol. 45, issued 15 June 1980, G. Spitzer et al., "High-Dose Combination Chemotherapy with Autologous Bone Marrow Transplantation in Adult Solid tumors," pages 3075-3085, see page 3079.	1-6,8-11,13,15
Y	J. Clin. Invest, Vol.70, issued December 1982, T. Nakahata et al.,, "Hemopoietic colony- joining cells... Progenitors" pages 1324-1328 see abstract	1-15

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 3

30 MAY 1991

Date of Mailing of this International Search Report

01 AUG 1991

International Searching Authority

ISA/US

Signature of Authorized Officer

SANDRA SAUCIER